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Originals

Idiopathic Hypercalciuria

Urate and Other Ions in Urine Before and on Various Long Term Treatments

H. S. Gill and G. A. Rose

St. Peter's Hospitals and Institute of Urology, London

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Summary. 24 h urine compositions of male stone formers with idiopathic hypercalciuria prior to treatment were compared with those of male general practitioners without urolithiasis. Urinary urate was slightly higher in the stone formers than in the normals but this was not statistically significant. Furthermore, when results were corrected for the higher creatinine excretions of the stone formers then the reverse was true and statistically significant. All subjects with urinary urate over 7.0 mmol/24 h were separately studied. In these groups the normals had higher urate and creatinine excretions than the stone formers but when results were corrected for creatinine the difference in the urate excretions disappeared. In long term follow up studies urinary calcium was lowered by diet and more so by diet supplemented with either Bendrofluazide or cellulose phosphate. Each drug raised urinary oxalate slightly and this was statistically significant, while both drugs together caused an even bigger rise in oxalate excretion. An unexpected finding was a rise in urinary urate with cellulose phosphate.

Key words: Hypercalciuria, Urate, Diet, Bendrofluazide, Cellulose phosphate.

Introduction

There is still dispute in the literature about the relationship between 24 h urinary calcium and urate on the one hand and calcium oxalate urolithiasis on the other hand. Some authors clearly find that urinary calcium is raised [1–5] and recognize the condition of idiopathic hypercalciuria, while other authors just as clearly find the urinary calcium to be normal [6–9] and only recognize idiopathic urolithiasis. It should be pointed out however, that the findings in the last two of these papers were equivocal since although mean 24 h urine calcium values were not significantly raised in the stone formers, each paper found the higher values only to occur in these patients. Some authors have found that urinary urate is raised in idiopathic hypercalciuria and idiopathic stone formers [10] but others have found this not to be so [9, 11–13]. This paper accepts that idiopathic hypercalciuria is a recogniseable entity and then concerns itself with whether or not urinary urate is raised in this condition. Part of the confusion could arise from the finding that stone formation is more common in the more affluent of the social classes [14] who spend more on food and therefore might have higher 24 h urinary values for urate, urea, and calcium than the general population. Hence the values for control non-stone formers should perhaps be taken not from the general population, but from the more affluent of the social classes. The present paper therefore, compares the 24 h urinary composition in idiopathic hypercalciuria with the findings previously recorded in a large group of doctors representing group one of the social economic classes.

A second part of the study is concerned with the long term changes occurring in urinary composition following treatment with low calcium and oxalate diet and with or without Bedrofluazide and/or cellulose phosphate.

Methods and Patients

The Medical Practitioners used as controls were selected and studied as previously described [15]. Results from males only were used. The patients were all attending the metabolic stone clinic and each had been followed for at least 3 years. Urine results for each patient were divided up into pre-treatment and treatment periods with each therapy. The mean values for each patient in each treatment period were calculated. The mean for each type of treatment was calculated from the mean for each patient.

Calcium was measured by flame spectrophotometry using an emission method [16] until May 1975 and atomic absorption [17] thereafter. Oxalate was measured by oxalate decarboxylase method [18] until February 1984, by automated oxalate oxidase method of Kasidas and Rose (1985) after July 1984, and by both methods in parallel from February to July 1984 and it was shown that the two methods gave the same results [19]. Urate was measured by phos-

Table 1. 24 h Urinary excretions of various chemicals in normal male doctors and in male stone-formers with idiopathic hypercalciuria

	A normal doctors $N = 295$	B stone-formers $N = 72$	C stone-formers per 14.22 nmol creatinine	p value for columns A & C	p value for columns A & B
Creatinine	14.22	17.7			<0.05
Calcium	5.09	11.23	9.02	<0.05	0.02
Phosphorus	19.60	36.30	29.16	0.5 n.s.	⩾0.05?
Urate	4.55	4.77	3.83	<0.05	>0.05 n.s.
Oxalate	0.28	0.33	0.27	<0.5 n.s.	>0.05 n.s.

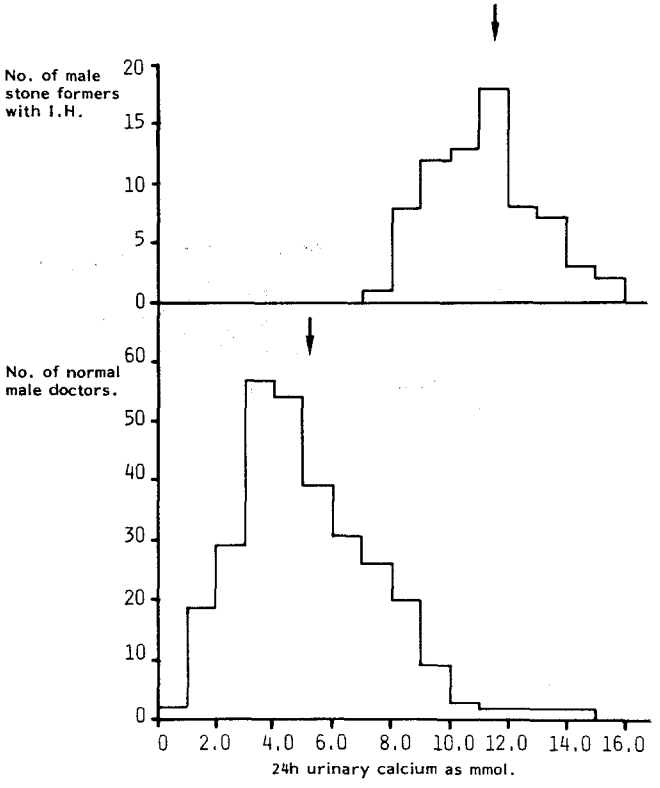

Fig. 1. Histograms for 24 h urinary calcium values in 295 normal male medical practitioners and 72 stone formers with idiopathic hypercalciuria

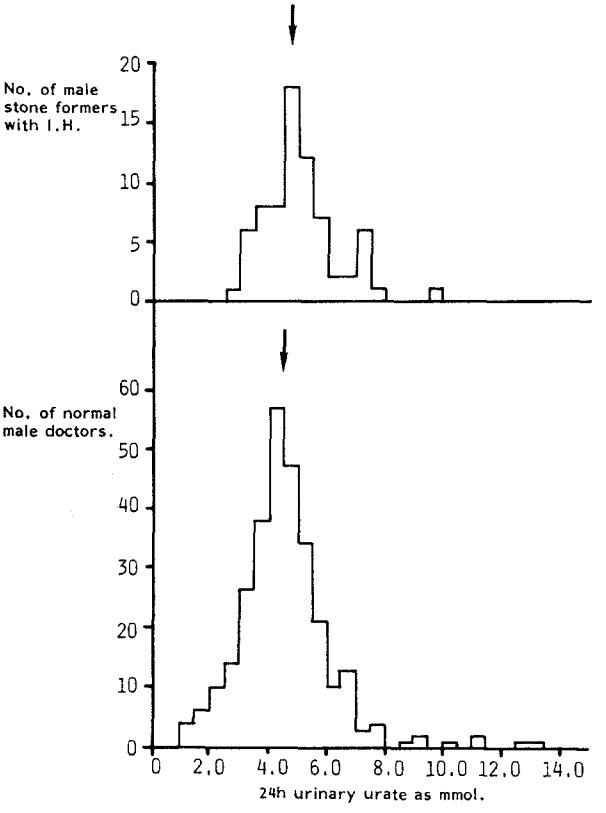

Fig. 2. Histograms for 24 h urinary urate values in 295 normal male medical practitioners and 72 male stone formers

photungstate method until May 1982 and by uricase method thereafter. Again there was no significant difference in values obtained by the two methods. Creatinine was measured by alkaline picrate method throughout and phosphate by the same colourimetric method throughout.

Results

The 24 h urinary compositions from 295 male doctors and 72 male stone formers with idiopathic hypercalciuria are shown in Table 1. Distributions of calcium and urate values are shown in Figs. 1 and 2 and it can be seen that these are non-Gaussian for normal urinary calcium as previously described [4] and slightly non-Gaussian for urinary urate in both normal and stone forming subjects. Despite this, "mean" values have been calculated and statistical analyses performed as if the distributions were all Gaussian and it is thought that no great distortions could have resulted. The normal subjects proved to have lower urinary creatinine values than the stone formers and the results for the latter have therefore been recalculated to allow for this. Each urinary value was expressed per 14.22 mmols of creatinine (the mean for the normals) and the mean for the group then calculated. The raw data showed that the stone formers had higher urinary calcium and oxalate values but the corrected

Table 2. 24 h Urinary excretions of various chemicals (and SD) in normal male doctors and in male stone-formers with idiopathic hypercalcuria, all having urinary urate values over 7.0 mmol

	A normal doctors $N = 15$	B stone-formers $N = 8$	C stone-formers per 14.22 mmol creatinine	D normal doctors per 14.22 mmol creatinine	p value for columns C & D	p value for columns A & B
Creatinine	23.8 (8.13)	19.6 (1.20)				
Calcium	7.96 (3.47)	13.05 (1.89)	9.49 (1.26)	5.44 (3.12)	>0.001	0.001
Phosphorus	58.27 (20.83)	46.90 (10.66)	33.75 (8.88)	5.79 (8.39)	<0.05	<0.05
Urate	9.15 (1.55)	7.65 (0.99)	5.55 (0.58)	5.89 (1.55)	0.02	<0.05
Oxalate	0.39 (0.11)	0.39 (0.11)	0.27 (0.06)	0.25 (0.11)	>0.05 n.s.	n.s.

Table 3. Effect on 24 h urinary composition of cellulose phosphate therapy in 11 patients

	A before treatment	B during treatment	p columns A & B	during treatment per 18.8 mmol creatinine	p columns A & C
Creatinine	18.8 ± 3.8	15.6 ± 3.2	0.02		
Calcium	11.1 ± 2.3	6.1 ± 1.8	0.001	7.35	<0.05
Phosphate	39.1 ± 15.8	42.7 ± 9.3	>0.05 n.s.	51.46	<0.05
Urate	4.8 ± 1.6	5.3 ± 1.0	0.05	6.39	<0.05
Oxalate	0.37 ± 0.10	0.33 ± 0.44	>0.1 n.s.	0.40	>0.05 n.s.

Table 4. Effect on 24 h urinary composition of bendrofluazide therapy in 45 patients

	A before treatment	B during treatment	p columns A & B	during treatment per 17.1 mmol creatinine	p columns A & C
Creatinine	17.1 ± 3.0	16.1 ± 3.1	0.1		
Calcium	11.2 ± 2.0	7.2 ± 1.8	0.001	7.65	<0.05
Phosphate	35.8 ± 7.7	33.5 ± 8.9	0.1 n.s.	35.58	>0.05 n.s.
Urate	4.91 ± 1.2	5.2 ± 1.3	<0.05	5.52	<0.05
Oxalate	0.30 ± 0.09	0.32 ± 0.07	>0.05 n.s.	0.34	0.05

Table 5. Effect on 24 h urinary composition of cellulose phosphate plus bendrofluazide therapy in 8 patients

	A before treatment	B after treatment	p for columns A & B	C during treatment per 19.2 mmol creatinine	p for columns A & C
Creatinine	19.2 ± 6.9	15.4 ± 3.2	0.01		
Calcium	10.4 ± 4.1	6.7 ± 1.8	<0.01	8.35	0.05
Phosphate	32.1 ± 1.8	41.9 ± 9.0	<0.05	52.24	<0.05
Urate	4.8 ± 1.4	5.1 ± 1.1	0.1 n.s.	6.36	<0.05
Oxalate	0.35 ± 0.12	0.38 ± 0.08	0.1 n.s.	0.47	<0.05

data showed that the urate values were actually lower in the stone formers.

Results from all individuals with urinary urate values above 7.0 mmol/24 h have been considered separately. There were 15 normal doctors and 8 patients who fell into this category and their results are shown in Table 2. Again they are expressed as raw data and also per 14.22 mmols of creatinine. The raw data shows that the stone formers had higher urinary calcium levels but lower urinary urate and phosphate levels than the normals. The creatinine cor-

Table 6. Effect on 24 h urinary composition of diet only in 8 patients

	A before treatment	B after treatment	p for columns A & B	C during treatment per 14.2 mmol creatinine	p for columns A & C
Creatinine	14.2 ± 2.9	15.7 ± 3.0	0.1		
Calcium	9.8 ± 2.6	8.1 ± 2.5	>0.01	7.33	<0.05
Phosphate	35.0 ± 7.8	33.1 ± 6.5	0.1 n.s.	29.94	0.05
Urate	4.5 ± 0.7	5.1 ± 0.8	>0.05	4.61	0.1 n.s.
Oxalate	0.38 ± 0.10	0.31 ± 0.07	0.05	0.28	<0.05

rected data shows that the stone formers still had higher urinary calcium levels but the differences in urate and phosphate disappeared.

The effects upon urinary composition of long-term treatment with cellulose phosphate and bendrofluazide, both of these, and diet alone are shown in Tables 3–6. Except in cases of diet alone mean urinary creatinine fell in every group presumably due to ageing and reduced food intake over the long period of time (3–18 years) of this study. Results have therefore been corrected to the mean pre-treatment urinary creatinine.

Discussion

Inspection of Fig. 1 and Table 1 shows that 24 h urinary urate is slightly higher in male hypercalciuric stone formers than in normal male medical practioners. However, higher values in the stone formers are also found for creatinine, phosphate and oxalate and the results should perhaps be corrected for urinary creatinine since it would seem that stone formers have greater mean muscle mass and therefore greater food intake. Table 1 shows that when such corrections are made the urinary urate is slightly lower in the stone formers than in the doctors while differences in phosphate and oxalate virtually disappear. The stone formers remain hypercalciuric although not as markedly so.

Figure 2 shows that the distribution of urinary urate is not quite Gaussian in either group both showing a "tail" at high levels. The group with urinary urate values above 7.0 mmol/24 h have therefore been considered separately. Table 2 shows that the 24 h urinary creatinine values in both of these groups are higher than in the corresponding groups of Table 1. In Table 2 therefore, both sets of results have been corrected to the mean creatinine of the normal doctors in Table 1. It is apparent that the corrected urate values are higher than the corrected values in Table 1 but again the normal doctors have a slightly higher mean value than the stone formers. Hence there seems to be no evidence in this study of hyperuricosuria amongst the stone formers and the reverse could be true. This seems to argue against the idea of trying to reduce urinary urate as a means of preventing calcium oxalate urolithiasis.

The normal urinary urate values given here might seem to be surprisingly high. However, it must be realised that just as normal plasma urate levels have risen considerably in developed countries in the last 30 years, and this is well documented and accepted, urinary urate values have also risen in parallel but this fact has not been well appreciated. Thus DeVries [20] has stated "in normal subjects on a unrestricted diet 24 h urinary excretion values between 1,100–1,200 mg" (6.5–7.1 mmols) "seem not to be rare in the experience of certain clinics". Hence, the values reported here for normal medical practitioners are in agreement with the values quoted in Israel.

This study of effects of treatment of urinary composition was longitudinal and occupied a period of many years. Hence the patients aged significantly and it is therefore not surprising that urinary creatinine should have fallen over the period. This was less marked and in fact absent in the case of treatment by diet alone, probably because this treatment was not maintained for long periods of time and many patients initially treated with diet alone either stopped attending or were later treated with drugs as well. It is also of interest that patients treated with diet alone had lower mean creatinine and calcium levels than the drug treated groups. In considering these results however, only the values corrected for creatinine will be used in order to avoid artefacts due to the ageing process.

Bendrofluazide treatment resulted in the expected clear fall in urinary calcium but there was a statistically significant rise in urinary oxalate which although small could be important. This effect has been noted before [21] but others have found the reverse [22] while yet others have found no change [23]. Urate excretion also rose after bendrofluazide, an effect that was not seen in other studies [23, 24]. Phosphate excretion was not changed on thiazide treatment.

Cellulose phosphate treatment also led a clear fall in urinary calcium (and magnesium, although this is not documented here). Urinary phosphate rose significantly presumably due to partial hydrolysis of cellulose phosphate [25], and although urinary oxalate rose as has been described before [26, 27] this did not achieve statistical significance, perhaps because of more rigid restriction of dietary oxalate [27]. It seems rather surprising however, to have found a

rise in urinary urate on cellulose phosphate to a mean value of 6.39 mmol/24 h and it is not easy to see why this should have occurred with this particular treatment and we are not aware that this change has been noted by any other group. Neither however, are we aware of any previous reports of the effect of cellulose phosphate upon urinary urate.

Hence the effects on urinary composition of thiazide and cellulose phosphate therapy are not all beneficial. Although either drug lowers urinary calcium each also raised urinary oxalate and it is difficult to be certain whether the first-state or end-state is better for stone formation. Cellulose phosphate also lowers urinary magnesium, an effect that was not studied here as it has been well described before [25]. This may be harmful to urolithiasis since magnesium inhibits calcium oxalate crystal formation in whole urine [28]. It is therefore important to know whether or not these drugs really reduce the incidence of urolithiasis and a separate study of this is in progress.

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Dr. G. A. Rose
St. Paul's Hospital
24 Endell Street
London, WC 2
England